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#9
MISC.
LETTER

TELEFAX CONTROL SHEET

SENT TO:

Examiner Henry Audet

DATE SENT:

8/5/03

SUBJECT:

09/736,076

No. of pages (including this cover sheet):

16

FROM:

Roger L. Browdy

Remarks:

CONFIDENTIALITY NOTE

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If this transmission is not well received, please advise us at our telecopier no. 202-737-3528 or by e-mail at mail@browdyneimark.com, or call our voice telephone no. 202-628-5197.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 98/ 10319	20/05/1998	21/05/1997
Applicant		
THE CHILDREN'S MEDICAL CENTER CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☒ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the title,
 - ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

Form PCT/ISA/210 (first sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 10319

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 50
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
Please see Further Information sheet enclosed.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

International Application No. PCT/ US 98 /10319

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The scope of claims 16 - 47 is very broad and speculative. A peptide sequence of which almost each of the 20 amino acids and the total length can vary independently, can not be considered to be a clear and concise definition of patentable subject matter. (Art.6 PCT).

Furthermore the available experimental data actually only comprise a very small amount of the compounds claimed. Therefor claims 16 - 47 can not be considered to represent a permissible generalisation which is fairly based on experimental evidence, that is, they are not adequately supported by the description (Art.6 PCT). Therefor a meaningful and economically feasible search could not encompass the complete subject-matter of the claims. Consequently the search has been limited to the actually tested compounds (Art.17(2)(a)(ii)PCT, PCT Guidelines III,2.1) and thus is only complete for claim 14.

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C12N9/12 C12Q1/48 A61K38/45

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GHISO J ET AL: "BINDING OF CYSTATIN C TO C4: THE IMPORTANCE OF SENSE-ANTISENSE PEPTIDES IN THEIR INTERACTION" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 87, no. 4, 1 February 1990, pages 1288-1291, XP000103571 see page 1289, left-hand column, paragraph 2 --- -/-	16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"3" document member of the same patent family

Date of the actual completion of the international search

29 October 1998

Date of mailing of the international search report

19/11/1998

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentlaan 2
 NL - 2200 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Van der Schaal, C

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US Accession no 109:69322, OKADA, YOSHIO ET AL: "Synthesis of Gln-Val-Val-Ala-Gly, a common sequence of thiol proteinase inhibitors, and its derivatives. Relationship between structure and effect on thiol proteinases" XP002082498 see abstract & PEPT. CHEM. (1988), VOLUME DATE 1987 653-6 CODEN: PECHDP;ISSN: 0388-3698,1988, ---</p>	16
A	<p>HARDIE G. AND HANKS S.: "The protein kinase factsbook I" 1995 , ACADEMIC PRESS , LONDON XP002082497 214500 cited in the application see page 7-20; figure 1 especially page 19 under Subdomain IX ---</p>	
A	<p>DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US Accession no 120:100177, MCMURRAY, JOHN S. ET AL: "Cyclic peptide substrates of pp60c-src: synthesis and evaluation" XP002082499 see abstract & INT. J. PEPT. PROTEIN RES. (1993), 42(3), 209-15 CODEN: IJPPC3;ISSN: 0367-8377,1993, ---</p>	2
A	<p>WO 97 14038 A (TERRAPIN TECH INC) 17 April 1997 see the whole document -----</p>	1,48,49

Information on patent family members

National Application No

PCT/US 98/10319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9714038 A	17-04-1997	US 5783405 A	21-07-1998
		US 5776716 A	07-07-1998
		AU 7398696 A	30-04-1997

Form PCT/ISA/210 (patent family annex) (July 1992)



Received from < 2027373528 > at 8/5/03 2:42:18 PM [Eastern Daylight Time]

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CMCC-590A PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/418)	
International application No. PCT/US98/10319	International filing date (day/month/year) 20/05/1998	Priority date (day/month/year) 21/05/1997	
International Patent Classification (IPC) or national classification and IPC C12N9/12			
Applicant THE CHILDREN'S MEDICAL CENTER CORPORATION et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 23 sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 25/11/1998		Date of completion of this report 13.09.99	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Pilat, D Telephone No. +49 89 2399 8668 	

Form PCT/IPEA/418 (cover sheet) (January 1994)

Received from < 2027373528 > at 8/5/03 2:42:18 PM [Eastern Daylight Time]

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/10319

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-16,18-33,36	as originally filed		
17,34,35	as received on	02/08/1999 with letter of	27/07/1999

Claims, No.:

1-51	with telefax of	27/08/1999
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Drawings, sheets:

1/21-21/21	as received on	02/08/1999 with letter of	27/07/1999
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2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-13, 15-51 partially, 14 completely.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/10319

because:

- ☒ the said international application, or the said claims Nos. 49,51 partially relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-13, 15-51 partially, 14 completely.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/10319

Ad Section I: Basis of the opinion

1. Reference is made to the following documents:

- D1: GHISO J ET AL: 'BINDING OF CYSTATIN C TO C4: THE IMPORTANCE OF SENSE-ANTISENSE PEPTIDES IN THEIR INTERACTION' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 87, no. 4, 1 February 1990, pages 1288-1291, XP000103571
- D3: DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US Accession no 120:100177, MCMURRAY, JOHN S. ET AL: 'Cyclic peptide substrates of pp60c-src: synthesis and evaluation' XP002082499 & INT. J. PEPT. PROTEIN RES. (1993), 42(3), 209-15 CODEN: IJPPC3;ISSN: 0367-8377,1993.

2) Amendments (Article 34 PCT)

- 2.1 The amended description page 17 line 11 reads: "the present invention also includes peptides having **"the sequence of"** with the proviso ... ". which has been modified to **"the sequence listed above"**.
When reading the whole application as filed, in particular p.16 lines 9-13, p.8 lines 16-37, claims 17,18,21,22,25,26,29,30,33,34,37,38,41,42,45,46, and the first and second sentence in this section, which shares an identical phrasing, it seems obvious that the truncated second sentence had to refer to the sequence listed in the first sentence of this section. The amendment complies with Article 34 PCT.
- 2.2 Fig.6E, which was part of the application as originally filed, shows a sequence ID N°55 (K035H001) with a N-terminal acetyl group. In response to the Invitation to furnish nucleotide and amino acid sequence listing, dated 8 July 1998, the applicant filed the 10 september 1998 a sequence listing containing a SEQ ID N°55 having a N-terminal "myristate". Thus, to correct the N-terminal indication of SEQ ID N°55 does not appear to infringe Article 34(2)(b) PCT.
- 2.3 Insofar as amended page17 appears to be supported (see also point 2.1a above), the amendment introduced in claim 15 is also supported and therefore complies with Article 34 (2)(b) PCT.

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EXAMINATION REPORT - SEPARATE SHEET

- 2.4 Fig.3 illustrate amino acid sequences of the HJ loop of PKC and xamples of conservative substitutions in these amino acid sequences. Claim 24 relates to a peptide corresponding to all the exemplified PKC substitutions. Therefore, Fig. 3 which refers to an additional glutamine in position AA₇ and AA₂₀ appears to support the amendment introduced in claim 24.

Ad Section IV :Lack of unity of invention

- 3.1 As far as claim 16 refers to a peptide with no functional requirement, the claimed subject-matter encompasses peptides which do not necessarily provide the same technical effect, or a technical effect at all. Accordingly, some of these peptides may not share any special technical features. The mere fact that they originate from a same serine threonine kinase loop cannot be considered as a special technical feature. The origin is neither a common functional nor a common structural feature of these peptides. Thus, the peptides claimed do not belong to the same invention.

For the same reasons the peptides within claims 20, 24, 28, 32, 36 40, 44 do not have an unifying special technical feature. As a consequence, neither the content of the individual claims listed above nor the group of claims as a whole can be considered as unitary (Unity, Article 34(3) Rules 13, 68 PCT).

Ad Section V :Reasoned statement under Rule 66.2(a)(ii); citations and explanations supporting such statement

- 4.1 The present invention characterizes a novel structural domain, called HJ loop, in serine threonine kinases. Said invention claims peptides comprising the entire HJ loop or subsequences of at least five amino acid residues of said HJ loop as well as peptide derivatives which can vary at one or two residues. Each claimed peptides have the function of modulating a serine threonine kinase (see claims 1 to 15).
- 4.2 Due to the nature of the claimed subject-matter, a complete search could not be carried out. Thus, as indicated in the PCT/ISA 210 forms, the search was limited to the compounds of claim 14. Clearly, no preliminary opinion can be expressed on unsearched matter. Hence this authority will only issue an prelliminary opinion

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with respect to claims 1 to 13 and 15 to 51 partially and claim 14 completely.

5. Novelty (Article 33 (2) PCT)**5.1 D3 describes Glu-Leu-Pro-Tyr-Ala-Gly and cyclo(Glu-Leu-Pro-Tyr-Ala-Gly).**

They have two amino acid residues at positions 2 and 5 which are different to the amino acid residues AA₈ and AA₁₁ of the corresponding subsequence AA₇-AA₁₂ in claim 25. Therefore, claim 25 is not novel.

It is emphasized that claims 25, 26 are not true dependent claims, insofar as they refer to only a part of the essential features enumerated in claim 24.

5.1 Claim 1 uses the expression "peptide derivative of HJ loop" and the "HJ loop". As far as these expressions are interpreted as defined in the present description at p.8 lines 5 to 37 and p.6 lines 10-35 respectively, none of the document cited in the international search report seems to anticipate the claimed subject-matter. Similarly, as far as dependent claims 7 and 15 having the proviso "that any one amino acid ... can vary" and claim 13 referring to a "subsequence" are interpreted based on the definition given in the present description, i.e. that "only one amino acid ... can vary" (see p.8 lines 21-32) and that it is "a contiguous sequence of from about five to about twenty amino acid residues" (p.8 lines 8-14), none of the document cited in the international search report seems to anticipate these peptides.

The same conclusion applies to the remaining dependent claims 2-6, 8-12, 14 and to independent claims 16 to 24 and 26 to 51.

6. Inventive step (Article 33 (3) PCT)

6.1 Claim 1 uses the expression "peptide derivative of HJ loop" and the "HJ loop". As far as the expression "peptide derivative of HJ loop" and the "HJ loop" are interpreted as defined in the present description at p.8 lines 5 to 37 and p.6 lines 10-35 respectively, none of the document cited in the International search report seem to suggest these peptides, taken alone or in any combination. Similarly, as far as dependent claims 7 and 15 having the proviso "that any one amino acid ... can vary" and claim 13 referring to a "subsequence" are interpreted based on the definition given in the present description, i.e. that "only one amino

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

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acid ... can vary" (see p.8 lines 21-32) and that it is "a contiguous sequence of from about five to about twenty amino acid residues" (p.8 lines 8-14), none of the document cited in the international search report seem to suggest these peptides, taken alone or in any combination.

The same conclusion applies to the remaining dependent claims 2-6,8- 12,14 and to independent claims 16 to 24 and 26 to 51.

7) Industrial applicability (Article 33 (4) PCT)

For the assessment of the present claims 49, 51 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Ad Section VIII : Certain observations on the international application.

The applicant is reminded that mutated serine/threonine kinase polypeptides (e.g. at the phosphorylated serine/threonine positions in said kinase or at any other essential residue) may anticipate present claim 1, insofar as they comprise a HJ loop, or a subsequence thereof, and modulate the serine/threonine kinase activity (e.g. by competition) (see p.18-19 bridging paragraph).

8. Clarity (Article 6 PCT)

8.1 By virtue of Article 6 PCT, the claims shall **define** the matter for which protection is sought and shall be clear and concise. Consequently, all the claims which are presently interpreted based on a definition given in the present description, because of ambiguous terminology, must be clarified, i.e. the loop identified by an arbitrary name "HJ loop", which is per se technically meaningless, should be characterized by means of technical features (see also point 6.1 above).

8.2 Claim 7 reads "**with the proviso that** one or two amino acids on the sequence of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

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the peptide can vary...". Both terms in the same sentence seem contradictory. All the claims using such a wording lack clarity.